

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

RUTTER, Keith  
SmithKline Beecham  
Two New Horizons Court  
Brentford, Middlesex, TW8 9EP  
ROYAUME-UNI

Date of mailing (day/month/year) 01 February 2002 (01.02.02)	<b>IMPORTANT NOTIFICATION</b>
Applicant's or agent's file reference AP/P32331	
International application No. PCT/EP00/05881	International filing date (day/month/year) 23 June 2000 (23.06.00)

## 1. The following indications appeared on record concerning:

☒ the applicant      ☐ the inventor      ☐ the agent      ☐ the common representative

## Name and Address

SMITHKLINE BEECHAM S.P.A.  
Via Zambelletti  
Baranzate de Bollate  
I-20021 Milan  
Italy

## State of Nationality

IT

## State of Residence

IT

Telephone No.

Facsimile No.

Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person      ☒ the name      ☒ the address      ☐ the nationality      ☐ the residence

## Name and Address

GLAXOSMITHKLINE S.P.A.  
Via Alessandro Fleming, 2  
I-37135 Verona  
Italy

## State of Nationality

IT

## State of Residence

IT

Telephone No.

Facsimile No.

Teleprinter No.

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

☒ the receiving Office      ☐ the designated Offices concerned  
☐ the International Searching Authority      ☒ the elected Offices concerned  
☐ the International Preliminary Examining Authority      ☐ other:

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer</p> <p>Elisabeth KÖNIG</p> <p>Telephone No.: (41-22) 338.83.38</p>
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## PCT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE  
 in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 01 February 2001 (01.02.01)	
<b>International application No.</b> PCT/EP00/05881	<b>Applicant's or agent's file reference</b> AP/P32331
<b>International filing date</b> (day/month/year) 23 June 2000 (23.06.00)	<b>Priority date</b> (day/month/year) 24 June 1999 (24.06.99)
<b>Applicant</b> FARINA, Carlo et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
 18 December 2000 (18.12.00)

☐ in a notice effecting later election filed with the International Bureau on:  
 \_\_\_\_\_

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Juan Cruz Telephone No.: (41-22) 338.83.38
---	---

## PATENT COOPERATION TREATY

10/019/05

PCT

From the INTERNATIONAL BUREAU

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

To:

RUTTER, Keith  
SmithKline Beecham  
Two New Horizons Court  
Brentford, Middlesex, TW8 9  
ROYAUME-UNI

TECH CENTER 1600-2900

APR 05 2002

RECEIVED

Date of mailing (day/month/year) 01 February 2002 (01.02.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference AP/P32331	
International application No. PCT/EP00/05881	International filing date (day/month/year) 23 June 2000 (23.06.00)

## 1. The following indications appeared on record concerning:

☒ the applicant    ☒ the inventor    ☐ the agent    ☐ the common representative

## Name and Address

GAGLIARDI, Stefania  
SmithKline Beecham S.p.A.  
Via Zambelletti sn  
Baranzate di Bollate  
I-20021 Milan  
Italy

## State of Nationality

IT

## State of Residence

IT

## Telephone No.

## Facsimile No.

## Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person    ☐ the name    ☒ the address    ☐ the nationality    ☐ the residence

## Name and Address

GAGLIARDI, Stefania  
NiKem Research S.r.L.  
Via Zambelletti, 25  
Baranzate di Bollate  
I-20021 Milan  
Italy

## State of Nationality

IT

## State of Residence

IT

## Telephone No.

## Facsimile No.

## Teleprinter No.

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

<input checked="" type="checkbox"/> the receiving Office	<input type="checkbox"/> the designated Offices concerned
<input type="checkbox"/> the International Searching Authority	<input checked="" type="checkbox"/> the elected Offices concerned
<input type="checkbox"/> the International Preliminary Examining Authority	<input type="checkbox"/> other:

The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Elisabeth KÖNIG

Telephone No.: (41-22) 338.83.38

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

RUTTER, Keith  
SmithKline Beecham  
Two New Horizons Court  
Brentford, Middlesex, TW8 9EP  
ROYAUME-UNIDate of mailing (day/month/year)  
01 February 2002 (01.02.02)Applicant's or agent's file reference  
AP/P32331

## IMPORTANT NOTIFICATION

International application No.  
PCT/EP00/05881International filing date (day/month/year)  
23 June 2000 (23.06.00)

## 1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

## Name and Address

FARINA, Carlo  
SmithKline Beecham S.p.A.  
Via Zambelletti  
Baranzate di Bollate  
I-20021 Milan  
Italy

## State of Nationality

IT

## State of Residence

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Telephone No.

Facsimile No.

Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

## Name and Address

FARINA, Carlo  
NiKem Research S.r.L.  
Via Zambelletti, 25  
Baranzate di Bollate  
I-20021 Milan  
Italy

## State of Nationality

IT

## State of Residence

IT

Telephone No.

Facsimile No.

Teleprinter No.

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned  
☐ the International Searching Authority ☒ the elected Offices concerned  
☐ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Authorized officer

Elisabeth KÖNIG

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

## PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

RUTTER, Keith  
SmithKline Beecham  
Two New Horizons Court  
Brentford, Middlesex, TW8 9EP  
ROYAUME-UNI

Date of mailing (day/month/year) 01 February 2002 (01.02.02)	<b>IMPORTANT NOTIFICATION</b>
Applicant's or agent's file reference AP/P32331	
International application No. PCT/EP00/05881	International filing date (day/month/year) 23 June 2000 (23.06.00)

## 1. The following indications appeared on record concerning:

☒ the applicant
 ☒ the inventor
 ☐ the agent
 ☐ the common representative

## Name and Address

 RAHMAN, Shahzad, Sharooq  
 SmithKline Beecham Pharmaceuticals  
 New Frontiers Science Park South  
 Third Avenue  
 Harlow  
 Essex CM19 5AW  
 United Kingdom

## State of Nationality

GB

## State of Residence

GB

## Telephone No.

## Facsimile No.

## Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person
 ☐ the name
 ☒ the address
 ☐ the nationality
 ☐ the residence

## Name and Address

 RAHMAN, Shahzad, Sharooq  
 GlaxoSmithKline  
 New Frontiers Science Park South  
 Third Avenue  
 Harlow  
 Essex CM19 5AW  
 United Kingdom

## State of Nationality

GB

## State of Residence

GB

## Telephone No.

## Facsimile No.

## Teleprinter No.

## 3. Further observations, if necessary:

## 4. A copy of this notification has been sent to:

☒ the receiving Office
 ☐ the designated Offices concerned  
☐ the International Searching Authority
 ☒ the elected Offices concerned  
☐ the International Preliminary Examining Authority
 ☐ other:

 The International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

## Authorized officer

Elisabeth KÖNIG

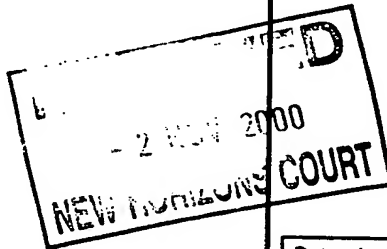
Telephone No.: (41-22) 338.83.38

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

## PCT

To:  
SMITHKLINE BEECHAM  
Attn. RUTTER, Keith  
Two New Horizons Court  
Brentford  
Middlesex TW8 9EP  
UNITED KINGDOM



NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference <b>AP/P32331</b>	Date of mailing (day/month/year) <b>03/11/2000</b>
International application No. <b>PCT/EP 00/05881</b>	International filing date (day/month/year) <b>23/06/2000</b>
Applicant <b>SMITHKLINE BEECHAM P.L.C.</b>	

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**  
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer <b>John De Bruijn</b>
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## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

**Letter (Section 205(b)):**

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (c ntinued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally the

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
 "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers;  
 claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
 "Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
 "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
 "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
 "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

**"Statement under article 19(1)" (Rule 46.4)**  
The amendments:

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims. It must be in the language in which the international application is published.

It must be in the language in which the international application is to be published.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been filed and the applicant has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

The applicant's attention is drawn to the fact that, where upon entering the national phase claims as amended under Article 19 are not filed, the international application for entry into the national phase is deemed to be withdrawn.

The applicant's attention is drawn to the fact that, where upon entry into the national phase claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated Office, please refer to the International Guide.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.



# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>AP/P32331</b>		<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/EP 00/05881</b>	International filing date (day/month/year) <b>23/06/2000</b>	(Earliest) Priority Date (day/month/year) <b>24/06/1999</b>	
Applicant <b>SMITHKLINE BEECHAM P.L.C.</b>			

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

### 1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**AZOLYL BENZAMIDES AND ANALOGUES AND THEIR USE FOR TREATING OSTEOPOROSIS**

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

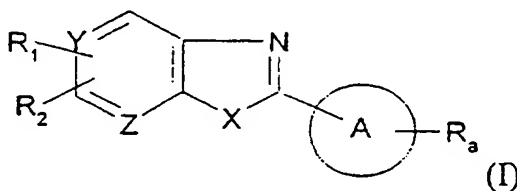
☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

## Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

A compound of formula (I)



or a salt thereof, or a solvate thereof, wherein;

X represents oxygen, sulphur, or  $\text{NR}_b$

Y and Z each independently represent nitrogen, CH,  $\text{CR}_1$  or  $\text{CR}_2$ ;

A represents an unsubstituted or substituted aryl group or an unsubstituted or substituted heterocyclyl group;

$\text{R}_a$  represents  $-\text{C}(\text{O})\text{NR}_s\text{R}_t$

$\text{R}_1$  and  $\text{R}_2$  each independently represents hydrogen or specific substituents;  
and the use of such a compound in the treatment and/or prophylaxis of  
diseases associated with over activity of osteoclasts in mammals.

## INTERNATIONAL SEARCH REPORT

International Application No

/EP 00/05881

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D235/18 C07D235/02 C07D401/12 C07D403/12 C07D409/04  
 C07D409/14 C07D453/02 C07D473/00 C07D471/04 A61K31/4184  
 A61K31/454 A61K31/4439 A61K31/437 A61K31/506 A61K31/52

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 12615 A (WARNER-LAMBERT COMPANY) 10 April 1997 (1997-04-10) the whole document, particularly examples 32 and 33 ---	1-3,5, 8-12,15
X	WO 95 30659 A (WARNER-LAMBERT COMPANY) 16 November 1995 (1995-11-16) cited in the application the whole document, particularly examples 18-20 ---	1-3,5, 9-12
X	US 4 093 726 A (WINN M ET AL) 6 June 1978 (1978-06-06) the whole document, particularly example VII --- -/--	1-3,5, 9-12

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

\* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

Date of the actual completion of the international search

13 October 2000

Date of mailing of the international search report

03/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Allard, M

## INTERNATIONAL SEARCH REPORT

International Application No

/EP 00/05881

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 A61P19/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	NOVELLI F ET AL: "Synthesis and biological investigations of 2-(tetrahydropyran-2'-yl) and 2-(tetrahydrofuran-2'-yl)benzimidazoles" IL FARMACO, vol. 52, no. 8-9, 1997, pages 499-507, XP002149935 the whole document, particularly page 500, compound 2	1-3,5, 8-12,15
X	TSUKAMOTO G ET AL: "Synthesis and antiinflammatory activity of some 2-(substituted-pyridinyl)benzimidazoles" JOURNAL OF MEDICINAL CHEMISTRY, vol. 23, no. 7, July 1980 (1980-07), pages 734-738, XP002149936 the whole document, particularly page 736, table I, compound 15	1-3,5, 9-12

-/--

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier document but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone  
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.  
 "&" document member of the same patent family

Date of the actual completion of the international search

13 October 2000

Date of mailing of the international search report

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Allard, M

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>✓ BARRACLOUGH P ET AL: "Inotropic 2-arylimidazol'1,2-a!pyrimidines" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 27, no. 3, 1992, pages 207-217, XP002149937 the whole document, particularly page 208, table I, compound 23, and page 209, scheme 1, compounds 4 and 15</p> <p>---</p>	1-3, 5, 9-12
X	<p>✓ KING F D: "Synthesis and thermal reactions of 1,2-dihydro-1,2,4-benzotriazines" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS I, no. 12, December 1988 (1988-12), pages 3381-3385, XP002149938 page 3382, compound (22)</p> <p>---</p>	1-3
X	<p>✓ FIGUET C ET AL: "Syntheses of segmental heteroleptic ligands for the self-assembly of heteronuclear helical supramolecular complexes" HELVETICA CHIMICA ACTA, vol. 77, no. 4, 29 June 1994 (1994-06-29), pages 931-942, XP002149939 page 934, compounds 8 and 9, page 935, compounds 12 and 13, and page 937, compound 21</p> <p>---</p>	1-3
X	<p>✓ DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002149940 Beilstein Registry Number 5988985 and 6009580 &amp; HETEROCYCLES, vol. 23, no. 6, 1985, pages 1425-1430,</p> <p>---</p>	1-3
X	<p>✓ DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002149941 Beilstein Registry Number 208984, 208985, 223809 and 298960 &amp; HELV. CHIM. ACTA, vol. 4, 1921, page 428, 429, 436</p> <p>---</p>	1-3
X	<p>✓ DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002149942 Beilstein Registry Number 42810 and 25528 &amp; GLAS. HEM. DRUS. BEOGRAD, vol. 21, 1956, page 95, 98</p> <p>---</p>	1-3

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## INTERNATIONAL SEARCH REPORT

International Application No

/EP 00/05881

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CROSSFIRE 'Online! Beilstein Institut zur Foerderung der Chemischen Wissenschaften; XP002149943 Beilstein Registry Number 6003643 & J. PRAKT. CHEM., vol. 331, no. 4, 1989, pages 649-658, ---	1-3
Y	FARINA C ET AL: "Selective inhibitors of vacuolar H <sup>+</sup> -ATPase of osteoclasts with bone antiresorptive activity" EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 9, no. 2, 1999, pages 157-168, XP000884849 ISSN: 1354-3776 the whole document ---	1-15
Y	WO 98 01436 A (SMITHKLINE BEECHAM S.P.A.) 15 January 1998 (1998-01-15) the whole document ---	1-15
P,Y	WO 99 33822 A (SMITHKLINE BEECHAMP LABORATOIRES PHARMACEUTIQUES) 8 July 1999 (1999-07-08) the whole document -----	1-15

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-3, 5, 8-12, 15 (all partly)

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty of the above mentioned claims. So many documents were retrieved that it is impossible to determine which parts of those claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). For these reasons it appears impossible to execute a meaningful search and/or to issue a complete search report over the whole breadth of the above mentioned claims.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 00/05881

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 6-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-3, 5, 8-12, 15 (all partly)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

T/EP 00/05881

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9712615	A	10-04-1997	AU 6966696 A	28-04-1997
			AU 7254196 A	28-04-1997
			US 5958950 A	28-09-1999
			US 6001866 A	14-12-1999
			WO 9712613 A	10-04-1997
			US 5972980 A	26-10-1999
WO 9530659	A	16-11-1995	US 5486517 A	23-01-1996
			AU 2197895 A	29-11-1995
			ZA 9503752 A	11-01-1996
US 4093726	A	06-06-1978	CA 1086725 A	30-09-1980
			FR 2372827 A	30-06-1978
			GB 1583357 A	28-01-1981
			JP 53071088 A	24-06-1978
WO 9801436	A	15-01-1998	EP 0912539 A	06-05-1999
			US 6025390 A	15-02-2000
WO 9933822	A	08-07-1999	AU 2715499 A	19-07-1999
			EP 1042316 A	11-10-2000
			NO 20003315 A	23-06-2000

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 15 JUN 2001

WIPO

PCT

14

Applicant's or agent's file reference <b>AP/P32331</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/EP00/05881</b>	International filing date (day/month/year) <b>23/06/2000</b>	Priority date (day/month/year) <b>24/06/1999</b>
International Patent Classification (IPC) or national classification and IPC <b>C07D235/18</b>		
Applicant <b>SMITHKLINE BEECHAM P.L.C.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 8 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand  <b>18/12/2000</b>	Date of completion of this report  <b>13.06.2001</b>
Name and mailing address of the international preliminary examining authority:   <b>European Patent Office</b> <b>D-80298 Munich</b> <b>Tel. +49 89 2399 - 0 Tx: 523656 epmu d</b> <b>Fax: +49 89 2399 - 4465</b>	Authorized officer  <b>Feiler, L</b>  Telephone No. <b>+49 89 2399 8282</b>



# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05881

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-81 as originally filed

**Claims, No.:**

1-15 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05881

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

## III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 6-8.

because:

- ☒ the said international application, or the said claims Nos. 6-8 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4, 6, 7, 13, 14
	No:	Claims	1-3, 5, 8-12, 15
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-5, 9-15

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/EP00/05881

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No:      Claims

2. Citations and explanations  
**see separate sheet**

**VI.      Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/EP00/05881

1. Claims 6-8 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

It has to be stressed that the search for Claims 1-3, 5, 8-12, 15 has been performed incompletely because the initial phase of the search already revealed a large number of novelty destroying documents.

The search for compounds having osteoplast/ osteoporosis related activity is complete.

**2. Cited Documents**

WO-A-9712515= D1

WO-A-9530659= D2

US-A-4093726= D3

Il Farmaco 52(1997), pp.499-507= D4

J. Med. Chem. 23(1980), pp. 734-738= D5

Europ. J. Med. Chem. 27(1992), pp. 207-217= D6

J. med Chem. 12 (1988), pp. 3381-3385= D7

Helv. Chim. Acta 77 (1994), 931-942= D8

Beilstein RN 5988985, 6009580 (1985)= D9

Beilstein RN 208984, 208985, 223809, 298960 (1921)= D10

Beilstein RN 42810, 25528 (1956)= D11

Beilstein RN 6003643 (1989)= D12

Expert Opinion on Therapeutic Patents 9 (1999)= D13

WO-A-9801436= D14

WO-A-9933822= D15

D15 is a P-document.

The indicated designation will be used throughout the examination procedure.

**3. Novelty**

The subject-matter of Claims 1-3; 5, 8-12, 15 is obviously not novel in view of :  
D1 (especially examples 32 and 33) and  
D4 (particularly page 500, compound 2).

The subject matter of Claims 1-3, 5, 9-12 is also not novel in view of :

D2 (particularly examples 18-20)

D3 (particularly example VII)

D5 (particularly page 736, table I, compound 15) and

D6 (particularly page 208, table I, compound 23 and page 209, scheme 1, compounds 4 and 15).

Subject matter of Claims 1-3 is also not novel in view of:

D7 (see page 3382, compound (22))

D8 (see page 934, compounds 8 and 9; page 935, compounds 12 and 13; page 937, compound 21)

D9-D12.

D13 refers to compounds useful to treat osteoporosis; these compounds which come structurally closest to those of the application are bicyclic heterocyclic structures differing from those of the application essentially due to the fact that they bear a side chain in 2-position whereas the compounds of the application have an aryl or heterocyclyl group directly bound to said 2-position.

Similarly the compounds of D14 differ from those of the application mainly due to the substituent in 2-position.

D15 discloses indole derivatives not considered according to the application.

The subject-matter claimed can therefore not be considered to be novel.

The following observations are valid for claims which do not comprise known matter.

#### **4. Inventive Step - Breadth of Claims**

##### **4.1 Subjective Problem**

According to the application (p. 1, sixth paragraph) the problem underlying the invention is to be seen in the provision of further compounds acting to selectively inhibit the bone resorbing activity of mammalian osteoclasts i.e. are useful to treat inter alia osteoporosis and related osteopenic diseases.

##### **4.2 Relevant and closest prior art**

Documents D1-D12 disclose compounds for which no or a pharmaceutical activity is disclosed which, as it appears, is different from acting on mammalian osteoclasts, so that those documents are not relevant for inventive step considerations. On the other hand D13 and D14 refer to the same medicinal activity and these documents are therefore relevant for the evaluation of inventive step. D15 may also be highly relevant on the condition that the claimed priority date is not valid. At present it is not possible to

check whether the priority date is acceptable or not, since the priority documents have not reached the examination file.

If the claimed priority date is justifiable D13 is considered to be closest prior art.

#### **4.3 Objectively solved problem**

The application documents contain insufficient information (the test methodology is disclosed but qualitative/quantitative test data for specific compounds are not given) upon which a judgement as to whether the technical problem according to point 3.1 has actually been solved or not by the claimed products is possible.

The information of page 81 is insufficient insofar as it has not been disclosed which specific compounds actually solve the above defined problem to a relevant extent.

For the time being it can only be said that the problem which has actually been solved is the provision of novel compounds.

#### **4.4 Evaluation of the solution of the problem**

D1-D12 disclose compounds structurally very similar to those of the present application so that the solution of the problem defined in point 4.3 must be considered to be obvious.

On the other hand those compounds which actually solve the problem defined in point 4.1 may be considered to be inventive since the structure of the compounds disclosed according D13 differs considerably from the one according to the application. If it turns out that D15 is to be taken into consideration (see above) a different evaluation may apply.

### **5. Industrial applicability**

For the assessment of the present claims 6-8 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.



## **6. Suggestions**

- In a possible national or regional examination phase an inventive step could nevertheless be acknowledged should information (preferably data) be submitted as to which specific compounds actually solve the technical problem defined in point 4.1.
- The breadth of Claim 1 should be such that it can be assumed that all the comprised possibilities actually solve the problem underlying the invention on which an inventive step could be based. It is to be stressed that generalisation of specific findings on which the acknowledgement of an inventive step could be based, is possible as far as **reasonable**. Certainly not reasonable are expressions like "substituted" or the expressions "aryl" and "heterocyclyl group" being undefined by a C-range and/or the possible heteroatoms.
- The description is to be adapted to new claims in the framework of the original disclosure.

Any examples and parts of the description no longer encompassed by the claims are to be deleted.

The documents cited in this communication should, insofar as this has not taken place, be referred to in the description with a short indication of their contents.

Pages amended in handwriting should also be submitted retyped.